America the Beautiful USA 15

SADMAN, STERNE, KESSLER & GOLDSTEIN
1225 Connecticut Avenue, N.W., Suite 300
Washington, D.C. 20036

0614.0690004

Applicant	: KENSIL, et al.	Docket:	
Serial No.	: 200,754		
Filed	: May 31, 1988	Attorney:	SLF/PAD
For	: SAPONIN ADJUVANT		

When receipt stamp is placed hereon, the USPTO acknowledges receipt of the following documents:

1. Information Disclosure Statement (pages 1-6)
2. Form PTO-1449 (pages 1-6)
3. Copies of references cited on Form PTO-1449 (21)

SAIDMAN, STERNE, KESSLER & GOLDSTEIN

ATTORNEYS AT LAW

1225 CONNECTICUT AVENUE
WASHINGTON, D.C. 20036
(202) 466-0800

CABLE: PRELEX
TELEX: 248636 SSK

TELEFAX: (202) 833-8716
GROUPS I, II & III

BALTIMORE
INNER HARBOR CENTER
400 EAST PRATT STREET, SUITE 800
BALTIMORE, MARYLAND 21202
(301) 659-7570

ROCKVILLE
25 WEST MIDDLE LANE
ROCKVILLE, MARYLAND 20850
(301) 251-8585

WRITER'S DIRECT NUMBER:

PERRY J. SAIDMAN
ROBERT GREENE STERNE
EDWARD J. KESSLER
JORGE A. GOLDSTEIN
SAMUEL L. FOX
HOLLIE L. BAKER
NEIL D. GERSHON*
HENRY N. WIXON*
DAVID K.S. CORNWELL*
MICHELLE PETERS*
JOHN D. MITCHELL, JR.*
SUSAN NEUBERGER WELLER
RICHARD M. LUDWIN*
PATRICIA A. DONOVAN*
JOAN L. DILLON

ABRAHAM BOGORAD
OF COUNSEL

RAYMOND C. GLENNY
JEFFREY I. AUERBACH
TRACY-GENE GRAVELINE
ROBERT W. ESMOND
SCOTT M. ALTER
REGISTERED
PATENT AGENTS

*BAR OTHER THAN D.C.

OIPE IAP89
AUG 25 2006
PATENT & TRADEMARK OFFICE

FILE COPY

December 13, 1988

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Re: U.S. Patent Application
Serial No.: 200,754; filed May 31, 1988
For: SAPONIN ADJUVANT
Our Ref: 0614.0690004

Sir:

The following documents are forwarded herewith for appropriate action by the Patent and Trademark Office:

1. Information Disclosure Statement (pages 1-6)

2. Form PTO-1449 (pages 1-6);

3. Copies of references cited on Form PTO-1449 (21); and

4. Return post card.

The Commissioner is hereby authorized to charge any fees that may be required to Deposit Account No. 19-0036. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

SAIDMAN, STERNE, KESSLER & GOLDSTEIN

Samuel L. Fox
Attorney for Applicant
30,353

SLF/PAD/hew
Enclosure

OIPE IAP69
AUG 25 2006
PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	:	
CHARLOTTE A. KENSIL et al.	:	Art Unit:
Serial No. 200,754	:	Examiner:
Filed: May 31, 1988	:	Atty Docket No. 0614.069.0004
For: SAPONIN ADJUVANT	:	

INFORMATION DISCLOSURE STATEMENT

Honorable Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

Submitted herewith on Form PTO-1449 is a listing of documents known to Applicants and/or their attorney in compliance with the requirements of 37 C.F.R. § 1.56. Copies of all documents cited herein also accompany this Information Disclosure Statement.

Applicants do not waive any rights to appropriate action to establish patentability over any of the listed documents should they be applied as references against the claims of the subject invention.

RELEVANCE OF THE DOCUMENTS

Reference AL, Japanese Patent Application No. 54-132218, October 15, 1979, discloses the separation of ginseng saponins by liquid chromatography using an adsorbent comprising a cross-linked

SAIDMAN, STERNE, KESSLER & GOLDSTEIN
ATTORNEYS AT LAW
1225 CONNECTICUT AVENUE
WASHINGTON, D.C. 20036
(202) 466-0800

polymerized gel, e.g., of starch cross-linked with divinyl-sulfone. An English abstract is provided.

Reference AM, Japanese Patent Application No. 61-007286A, January 13, 1986, discloses the isolation of saponins from soybean seeds using column chromatography. An English abstract is provided.

Reference AA, U.S. Patent No. 4,335,113, June 15, 1982, discloses the extraction of saponin from chrysanthellums by high pressure liquid chromatography.

Reference AB, U.S. Patent No. 4,524,067, June 18, 1985, discloses saponins isolated from soybean seeds wherein extracts are purified with high-pressure liquid chromatography.

Document AR1, Dalsgaard, K., referred to on page 3 of the Specification, discloses the partial purification of an aqueous extract of the saponin adjuvant material from the bark of the tree, Quillaja saponaria Molina, by a combination of gel exclusion and ion exchange chromatography. The disclosed preparation which is commercially available under the name "Quil-A," is characterized chemically as a carbohydrate moiety in glycosidic linkage to the triterpenoid quillaic acid. One of the partially purified fractions, separated by a combination of gel exclusion and ion exchange chromatography, exhibited adjuvant activity in foot-and-mouth disease vaccines in guinea pigs and cattle. It was also disclosed that the active fraction in aqueous solution is present in a micellar state above a critical micellar concentration, and that this property of forming micelles creates an aggregation of monomers that are difficult to separate by standard physical-chemical methods.

SAIDMAN, STERNE, KESSLER & GOLDSTEIN
ATTORNEYS AT LAW
1225 CONNECTICUT AVENUE
WASHINGTON, D.C. 20036
(202) 466-0800

Document AS1, Higuchi et al., referred to on page 3 of the Specification, discloses the structure of two desacylsaponins isolated from the bark of Quillaja saponaria Molina by weak alkali. The desacylsaponins were identified as quillaic acid 3,28-O-bisglycosides, each containing eight monosaccharides in glycosidic linkage. Neither the purity nor the biological activity of the desacylsaponins is disclosed.

Reference AT1, Higuchi and Komori, referred to on page 3 of the application, discloses that mild alkaline hydrolysis of the triterpenoid saponin mixture obtained from the bark of Quillaja saponaria produces, as two major products, two desacylsaponins (quillaic acid 3, 28-O-bisglycosides), together with less polar compounds (eliminated acyl groups). This reference also discloses the isolation and structure of the eliminated acyl groups that originated from the acyl moieties of Quillaja saponaria. No biological activity was ascribed to the compounds.

Reference AR2, Dalsgaard, K., referred to on page 8 of the application, is a review article discussing the isolation and characterization of the saponin Quil-A and the evaluation of its adjuvant activity, with special reference to the application of the saponin in the vaccination of cattle against foot-and-mouth disease.

Reference AS2, Scott, et al. referred to on page 8 of the application, discloses studies using ^{125}I-labelled KLH which show that saponins significantly prolong the retention of antigens at a subcutaneous injection site and also increase the amount reaching the spleen. Both phenomenon were associated with inflammatory responses

SAIDMAN, STERNE,
KESSLER & GOLDSTEIN
ATTORNEYS AT LAW
1225 CONNECTICUT AVENUE
WASHINGTON, D C 20036
(202) 466-0800

to saponin and were markedly reduced following abolition of the inflammatory action of the saponin by addition of cholesterol-containing liposomes. Adjuvant activity was not modified by this treatment.

Reference AT2, Higuchi et al., discloses the characterization of a major component of Quillaja saponin, 3,28-O-bisglycoside. The investigators obtained saponin from the bark of Quillaja saponaria Molina and fractionated it by droplet counter current chromatography (DCCC) and reverse-phase chromatography to isolate the major component named QS-III.

Reference AR3, Petermann et al., is an abstract which discloses that inactive anti-rabies cattle vaccine is potentiated by saponin with or without $Al(OH)_3$. The potentiation occurred when both the adjuvant and the lyophilized vaccine were injected simultaneously but separately and also when the adjuvant was incorporated into the liquid vaccine before administration.

Reference AS3, Bomford, R., discloses evidence supporting the hypothesis that the adjuvant, as well as the hemolytic activity of saponin, depends on binding to cholesterol in cell membranes.

Reference AT3, Nagasawa et al., discloses the application of high-performance liquid chromatography to the isolation of ginsenoside-Rb_1-Rb_2-Rc-Rd-Re-Rg_1 from ginseng saponins.

Reference AR4, Zhou et al., discloses the isolation by means of reverse phase high-performance liquid chromatography of two ginseng saponins, notoginsenosides-R1 and -R2 and the establishment of their structures by ^{13}C magnetic resonance spectroscopy and mass spectrometry. Two other known saponins ginsenosides-H1 and -RG2, which were

SAIDMAN, STERNE, KESSLER & GOLDSTEIN
ATTORNEYS AT LAW
1225 CONNECTICUT AVENUE
WASHINGTON, D.C. 20036
(202) 466-0800

previously isolated from ginseng roots, were also isolated and identified.

Reference AS4, Bomford, R., discloses studies on the cellular site of action of the adjuvant activity of saponin for sheep erythrocytes. The data showed that attachment of the saponin to the antigen is not essential, suggesting that the adjuvant effect, which is T-cell dependent, is exerted on host cells in the draining lymph node.

Reference AT4, Bomford, R., discloses a comparison of the relative adjuvant efficacy of $Al(OH)_3$ and saponin as related to the immunogenicity of the antigen.

Reference AR5, Morein et al., discloses the use of Quil-A in the development of ISCOMS, structures for antigenic presentation of membrane proteins from enveloped viruses.

Reference AS5, Strobbe et al., cited in the PCT International Search Report for a related application, discloses studies on the adjuvant activity of saponin fractions in foot-and-mouth disease vaccine. The fractionated saponin was saponin purum album from Merck.

Reference AT5, Mostad and Doehl, cited in the PCT International Search Report for a related application, discloses separation and characterization of oleanene-type pentacyclic triterpenes from Gypsophila arrostii by liquid chromatography and mass spectrometry.

Reference AR6, Egerton et al., cited in the PCT International Search Report for a related application, discloses that aluminum precipitated Bacteriodes nodosus vaccines prepared from two antigens with and without the saponin derivative, Quil-A, did not induce

SAIDMAN, STERNE, KESSLER & GOLDSTEIN
ATTORNEYS AT LAW
1225 CONNECTICUT AVENUE
WASHINGTON, D.C. 20036
(202) 466-0800

adverse tissue reactions in sheep. Vaccinated, non-infected Merino sheep had higher agglutination antibody titers when the vaccines included Quil-A. Moreover, the recovery rates in vaccinated sheep affected with foot-rot were higher when the vaccines included Quil-A.

Reference AS6, McColm et al., cited in the PCT International Search Report for a related application, discloses a comparison of saponin with other adjuvants for the potentiation of protective immunity by a killed Plasmodium yoelii vaccine in the mouse.

REMARKS

This statement should not be construed as a representation that more material information does not exist or that an exhaustive search of the relevant art has been made.

Consideration of the cited documents and making the same of record in the prosecution of the above-identified application are respectfully requested.

Respectfully submitted,

SAIDMAN, STERNE, KESSLER & GOLDSTEIN

Samuel L. Fox

Samuel L. Fox
Attorney for Applicant
Registration No. 30,353

Date: December 13, 1988

P52-39.WP

SAIDMAN, STERNE,
KESSLER & GOLDSTEIN
ATTORNEYS AT LAW
1225 CONNECTICUT AVENUE
WASHINGTON, D.C. 20036
(202) 466-0800

FORM PTO-1449

INFORMATION DISCLOSURE STATEMENT

Atty Docket	Serial No.
0614.0690004	200,754
Applicant: KENSIL, et al.	
Filing Date: May 31, 1988	Group:

OIPE IAP68 AUG 9, 2006 PATENT & TRADEMARK OFFICE

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Sub-class	Filing Date
	AA	4,333,913	06/15/82	Combier et al.			
	AB	4,524,067	06/18/85	Arichi et al.			
	AC	, ,	/ /				
	AD	, ,	/ /				
	AE	, ,	/ /				
	AF	, ,	/ /				
	AG	, ,	/ /				
	AH	, ,	/ /				
	AI	, ,	/ /				
	AJ	, ,	/ /				
	AK	, ,	/ /				

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Sub-class	Translation
	AL	54-132218	10/15/79	JAPAN			Yes / No
	AM	61-007286A	01/13/86	JAPAN			Yes / No
	AN		/ /				Yes / No
	AO		/ /				Yes / No
	AP		/ /				Yes / No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	1	Dalsgaard, K., Archive fÜr die gesamte Virusforshung 44:243-254 (1974)
	AS	1	Higuchi et al., Phytochemistry, 26 (1): 229-235 (1987)
	AT	1	Higuchi and Komori, Phytochemistry, 26 (8): 2357-2360 (1987)

Examiner | Date Considered

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

FORM PTO-1449

INFORMATION DISCLOSURE STATEMENT

Atty Docket	Serial No.
0614.0690004	200,754
Applicant: KENSIL, et al.	
Filing Date: May 31, 1988	Group:

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Sub-class	Filing Date
	AA	, ,	/ /				
	AB	, ,	/ /				
	AC	, ,	/ /				
	AD	, ,	/ /				
	AE	, ,	/ /				
	AF	, ,	/ /				
	AG	, ,	/ /				
	AH	, ,	/ /				
	AI	, ,	/ /				
	AJ	, ,	/ /				
	AK	, ,	/ /				

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Sub-class	Translation
	AL		/ /				Yes / No
	AM		/ /				Yes / No
	AN		/ /				Yes / No
	AO		/ /				Yes / No
	AP		/ /				Yes / No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	2	Dalsgaard, K., Acta Veterinari Scandinavica (Suppl.) 69:1-40 (1978)
	AS	2	Scott et al., Int. Archs Allergy appl. Immun. 77:409-412 (1985)
	AT	2	Higuchi et al., Phytochemistry 27 (4): 1165-1168 (1988)

Examiner | Date Considered

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

FORM PTO-1449

INFORMATION DISCLOSURE STATEMENT

Atty Docket	Serial No.
0614.0690004	200,754
Applicant: KENSIL, et al	
Filing Date: May 31, 1988	Group:

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Sub-class	Filing Date
	AA	, ,	/ /				
	AB	, ,	/ /				
	AC	, ,	/ /				
	AD	, ,	/ /				
	AE	, ,	/ /				
	AF	, ,	/ /				
	AG	, ,	/ /				
	AH	, ,	/ /				
	AI	, ,	/ /				
	AJ	, ,	/ /				
	AK	, ,	/ /				

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Sub-class	Translation
	AL		/ /				Yes / No
	AM		/ /				Yes / No
	AN		/ /				Yes / No
	AO		/ /				Yes / No
	AP		/ /				Yes / No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	3	Petermann, H.G. et al., Chemical Abstracts, 72:198, 88330c (1970)
	AS	3	Bomford, R., Int. Archs Allergy Appl. Immun. 63:170-177 (1980)
	AT	3	Nagasawa et al. Chem. Pharm. Bull. 28(7):2059-2064 (1980)

Examiner | Date Considered

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

FORM PTO-1449

INFORMATION DISCLOSURE STATEMENT

Atty Docket	Serial No.
0614.0690004	200,754
Applicant: KENSIL, et al.	
Filing Date: May 31, 1988	Group:

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Sub-class	Filing Date
	AA	, ,	/ /				
	AB	, ,	/ /				
	AC	, ,	/ /				
	AD	, ,	/ /				
	AE	, ,	/ /				
	AF	, ,	/ /				
	AG	, ,	/ /				
	AH	, ,	/ /				
	AI	, ,	/ /				
	AJ	, ,	/ /				
	AK	, ,	/ /				

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Sub-class	Translation
	AL		/ /				Yes No
	AM		/ /				Yes No
	AN		/ /				Yes No
	AO		/ /				Yes No
	AP		/ /				Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	4	Zhou et al., Chem Pharm. Bull 29 (10):2844-2850 (1981)
	AS	4	Bomford, R., Int. Archs Allergy Appl. Immun. 63:127-131 (1982)
	AT	4	Bomford, R., Int. Archs Allergy appl. Immun. 75:280-281 (1984)

Examiner | Date Considered

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

FORM PTO-1449

INFORMATION DISCLOSURE STATEMENT

Atty Docket	Serial No.
0614.0690004	200,754
Applicant: KENSIL, et al.	
Filing Date: May 31, 1988	Group:

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Sub-class	Filing Date
	AA	, ,	/ /				
	AB	, ,	/ /				
	AC	, ,	/ /				
	AD	, ,	/ /				
	AE	, ,	/ /				
	AF	, ,	/ /				
	AG	, ,	/ /				
	AH	, ,	/ /				
	AI	, ,	/ /				
	AJ	, ,	/ /				
	AK	, ,	/ /				

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Sub-class	Translation
	AL		/ /				Yes / No
	AM		/ /				Yes / No
	AN		/ /				Yes / No
	AO		/ /				Yes / No
	AP		/ /				Yes / No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	5	Morein et al., Nature 308:457-460 (1984)
	AS	5	Strobbe et al., Arch. Exper. Vet. Med. 28:385-392 (1974)
	AT	5	Mostad and Doehl, J. of Chromatography 396:157-168 (1987)

Examiner | Date Considered

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

FORM PTO-1449

INFORMATION DISCLOSURE STATEMENT

Atty Docket	Serial No.
0614.0690004	200,754
Applicant: KENSIL, et al.	
Filing Date: May 31, 1988	Group:

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Sub-class	Filing Date
	AA	, ,	/ /				
	AB	, ,	/ /				
	AC	, ,	/ /				
	AD	, ,	/ /				
	AE	, ,	/ /				
	AF	, ,	/ /				
	AG	, ,	/ /				
	AH	, ,	/ /				
	AI	, ,	/ /				
	AJ	, ,	/ /				
	AK	, ,	/ /				

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Sub-class	Translation
	AL		/ /				Yes No
	AM		/ /				Yes No
	AN		/ /				Yes No
	AO		/ /				Yes No
	AP		/ /				Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	6	Egerton et al., Vet. Sci. Comm., 2:247-252 (1978)
	AS	6	McColm et al., Parasite Immun. 4:337-347 (1982)

Examiner | Date Considered

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.